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WHAT IS CLAIMED IS:

1. A method for evaluating specificity of a drug comprising comparing activity of said drug against its target pathway (D_{target}) in a biological sample and activity of said drug against at least one off-target pathway ($D_{off-target}$) in said biological sample.
2. The method of Claim 1 wherein said D_{target} and $D_{off-target}$ are measured according to a method comprising:
 - a) applying a plurality of levels of said drug to said biological sample and measuring a plurality of cellular constituents in said biological sample at each level of said drug to obtain a first profile of graded drug response;
 - b) applying said plurality of levels of said drug to a test sample, wherein said test sample is the same as said biological sample except that said target pathway is not functional, and measuring said plurality of cellular constituents in said test sample at each level of said drug to obtain a second profile of graded drug response; and
 - c) determining said D_{target} and $D_{off-target}$ by comparing said first and second profiles.
3. The method of claim 2 wherein said biological sample is a yeast cell and said test sample is a yeast cell with a critical gene in said target pathway being deleted.
4. The method of claim 2 wherein said biological sample is a mammalian cell and said test sample is a mammalian cell with a critical gene in said target pathway being deleted.
5. The method of claim 2 wherein said biological sample is an animal and said test sample is a transgenic animal with a critical gene in said target pathway being made nonfunctional.
6. The method of claim 2 wherein said plurality of cellular constituents are transcripts of a plurality of genes.
7. The method of claim 2 wherein said plurality of cellular constituents are proteins.
8. The method of claim 1 wherein said D_{target} and $D_{off-target}$ are measured according to a method comprising:

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a) perturbing said target pathway and/or said off target pathway in said biological sample to obtain a perturbation profile consisting of a plurality of cellular constituent measurements;

b) applying a plurality of levels of said drug to said biological sample to obtain a drug response profile consisting of a plurality of cellular constituent measurements at each level of said drug; and

c) decomposing said D_{target} and $D_{off-target}$ by comparing said drug response profile and said perturbation profile.

10 9. The method of claim 8 wherein said plurality of cellular constituents are transcripts of a plurality of genes.

10. The method of claim 8 wherein said plurality of cellular constituents are proteins.

15 11. The method of claim 1 wherein said determining step comprises calculating a specificity index (SI) according to the following formulae:

$$SI = \frac{n \cdot D_{target}}{\sum D_{off-target}}$$

20 wherein: n is the number of said off-target pathways.

12. A method for evaluating specificity of a drug comprising:

a) measuring activity of said drug against its target pathway to obtain a target activity (D_{target});

b) measuring activity of said drug against at least one pathway other than said target pathway to obtain at least one off-target activity ($D_{off-target}$); and

c) determining said specificity by comparing said target activity and said off-target activity.

30 13. The method of claim 12 wherein said D_{target} and $D_{off-target}$ are measured according to a method comprising:

a) applying a plurality of levels of said drug to said biological sample and measuring a plurality of cellular constituents in said biological sample at each level of said drug to obtain a first profile of graded drug response;

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b) applying said plurality of levels of said drug to a test sample, wherein said test sample is the same as said biological sample except that said target pathway is not functional, and measuring said plurality of cellular constituents in said test sample at each level of said drug to obtain a second profile of graded drug response; and

5 c) determining said D_{target} and $D_{off-target}$ by comparing said first and second profiles.

14. The method of claim 13 wherein said plurality of cellular constituents are transcripts of a plurality of genes.

10 15. The method of claim 13 wherein said plurality of cellular constituents are proteins.

16. The method of claim 13 wherein said biological sample is a yeast cell and said test sample is a yeast cell with a critical gene in said target pathway being deleted.

15 17. The method of claim 13 wherein said biological sample is a mammalian cell and said test sample is a mammalian cell with a critical gene in said target pathway being deleted.

18. The method of claim 13 wherein said biological sample is an animal and said test sample is a transgenic animal with a critical gene in said target pathway being made
20 nonfunctional.

19. The method of claim 12 wherein said D_{target} and $D_{off-target}$ are measured according to a method comprising:

a) perturbing said target pathway and/or said off target pathway in said biological
25 sample to obtain a perturbation profile consisting of a plurality of cellular constituent measurements;

b) applying a plurality of levels of said drug to said biological sample to obtain a drug response profile consisting of a plurality of cellular constituent measurements at each level of said drug; and

30 c) decomposing said D_{target} and $D_{off-target}$ by comparing said drug response profile and said perturbation profile.

20. The method of claim 19 wherein said plurality of cellular constituents are transcripts of a plurality of genes.

21. The method of claim 20 wherein said plurality of cellular constituents are proteins.

22. The method of claim 12 wherein said determining step comprises calculating a specificity index (SI) according to the following formulae:

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$$SI = \frac{n \cdot D_{target}}{\sum D_{off-target}}$$

wherein: n is the number of said off-target pathways.

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23. A method of determining therapeutic index of a drug in a biological sample comprising:

determining said therapeutic index according to the formula: $SI = C_{target} / C_{off-target}$,
wherein C_{target} is a minimum effective concentration needed to induce a threshold response
in a target pathway and $C_{off-target}$ is the minimum toxic concentration needed to induce a
threshold response in at least one off-target pathway.

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24. The method of claim 23 wherein said C_{target} and $C_{off-target}$ are measured according to a
method comprising:

20 a) applying a plurality of levels of said drug to said biological sample and measuring a
plurality of cellular constituents at each level of said drug in said biological sample to
obtain a first profile of graded drug response;

b) applying said plurality of levels of said drug to a test sample, wherein said test
sample is the same as said biological sample except that said target pathway is not
functional, and measuring a plurality of cellular constituents in said test sample at each
level of said drug, to obtain a second profile of graded drug response; and

c) determining said C_{target} and $C_{off-target}$ by comparing said first and second profiles.

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26. The method of claim 24 wherein said plurality of cellular constituents are transcripts of
a plurality of genes.

27. The method of claim 24 wherein said plurality of cellular constituents are proteins.

28. The method of claim 24 wherein said biological sample is a yeast cell and said test
sample is a yeast cell with a critical gene in said target pathway being deleted.

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28. The method of claim 24 wherein said biological sample is a mammalian cell and said test sample is a mammalian cell with a critical gene in said target pathway being deleted.

29. The method of claim 24 wherein said biological sample is an animal and said test sample is a transgenic animal with a critical gene in said target pathway being made nonfunctional.

30. The method of claim 24 wherein said target threshold response is at least two fold induction or repression of a plurality of cellular constituents in said target pathway.

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31. The method of claim 24 wherein said off-target threshold response is at least two fold induction or repression of a plurality of cellular constituents in said off-target pathway.

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32. The method of claim 23 wherein said target threshold response is a response that is sufficient to have a therapeutic effect.

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33. The method of claim 23 wherein said off-target threshold response is a response that is sufficient to constitute a toxic effect.

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34. A method of determining a therapeutic index of a drug in a biological sample comprising:

- a) applying a plurality of levels of said drug to said biological sample;
- b) determining a minimum effective concentration (C_{target}) needed to induce a threshold response in a target pathway, wherein said drug exerts its pharmacological activity through said target pathway;
- c) determining a minimum toxic concentration ($C_{off-target}$) needed to induce a threshold response in at least one off-target pathway; and
- d) determining said therapeutic index according to the formula: $SI = C_{target} / C_{off-target}$.

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35. The method of claim 34 wherein said C_{target} and $C_{off-target}$ are measured according to a method comprising:

- a) applying a plurality of levels of said drug to said biological sample and measuring a plurality of cellular constituents at each level of said drug in said biological sample to obtain a first profile of graded drug response;

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b) applying said plurality of levels of said drug to a test sample, wherein said test sample is the same as said biological sample except that said target pathway is not functional, and measuring a plurality of cellular constituents in said test sample at each level of said drug to obtain a second profile of graded drug response; and

5 c) determining said C_{target} and $C_{off-target}$ by comparing said first and second profiles.

36. The method of claim 35 herein said plurality of cellular constituents are transcripts of a plurality of genes.

10 37. The method of claim 35 wherein said plurality of cellular constituents are proteins.

38. The method of claim 35 wherein said biological sample is a yeast cell and said test sample is a yeast cell with a critical gene in said target pathway being deleted.

15 39. The method of claim 36 wherein said biological sample is a mammalian cell and said test sample is a mammalian cell with a critical gene in said target pathway being deleted.

40. The method of claim 36 wherein said biological sample is an animal and said test sample is a transgenic animal with a critical gene in said target pathway being made

20 nonfunctional.

41. The method of claim 35 wherein said target threshold response is at least two fold induction or repression of a plurality of cellular constituents in said target pathway.

25 42. The method of claim 35 wherein said off-target threshold response is at least two fold induction or repression of a plurality of cellular constituents in said off-target pathway.

43. The method of claim 35 wherein said target threshold response is a response that is sufficient to have a therapeutic effect.

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44. The method of claim 35 wherein said off-target threshold response is a response that is sufficient to constitute a toxic effect.

45. A method for monitoring a therapy for a patient using a drug comprising:

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comparing activity of said drug on its target pathway (D_{target}) and at least one off target pathway ($D_{off-target}$) in said patient.

46. The method of claim 45 wherein said D_{target} and $D_{off-target}$ are determined according to a
5 method comprising:

- a) measuring a plurality of cellular constituents in said patient to obtain a drug response profile;
- b) perturbing said patient with a plurality of pathway perturbations to obtain a plurality of pathway perturbation profiles; and
- 10 c) decomposing said drug response profile into said D_{target} and $D_{off-target}$.

47. The method of claim 46 wherein said cellular constituents are transcripts of genes.

48. The method of claim 46 wherein said cellular constituents are proteins.
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49. The method of claim 46 wherein said decomposing comprises representing said drug response profile with said pathway perturbation profiles.

50. A method for monitoring a therapy for a patient comprising
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- a) measuring a plurality of cellular constituents in said patient to obtain a drug response profile, wherein said patient is undergoing a treatment with a drug;
- b) perturbing said patient with a plurality of pathway perturbations to obtain a plurality of pathway perturbation profiles;
- c) decomposing said drug response profile into a plurality of pathway response profiles
25 using said pathway perturbation profiles; and
- d) determining relative activity of said drug on its target pathway and at least one off-target pathway.

51. The method of 50 wherein said cellular constituents are transcripts of genes.
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52. The method of 50 wherein said cellular constituents are proteins.

53. The method of claim 50 wherein said decomposing comprises representing said drug response profile with said pathway perturbation profiles.
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54. A method for determining a dose of a drug for a patient comprising;
determining a dose that has a relatively high activity on a target pathway and relatively low activity on at least one off-target pathway relative to one or more other doses.

5 55. The method of claim 54 wherein said activity on target pathway (D_{target}) and said activity on at least one off-target pathway ($D_{off-target}$) are determined according to a method comprising:

- a) applying a plurality of levels of a plurality of pathway perturbations to said patient;
- b) determining a plurality of cellular constituent responses in said patient to obtain 10 perturbation profiles;
- b) applying a plurality of levels of said drug to said patient;
- c) determining a plurality of cellular constituent responses in said patient to obtain a drug response profile; and
- d) decomposing said drug response profile to pathway responses using said plurality of 15 perturbation profiles to obtain said D_{target} and said $D_{off-target}$.

56. The method of claim 55 wherein said cellular constituents are transcripts of genes.

57. The method of claim 55 wherein said cellular constituents are proteins.

20 58. The method of claim 55 wherein said plurality of levels of said drug and pathway perturbations are non-toxic to said patient.

59. A method for determining an optimal dose of a drug for a patient comprising:
25 a) applying a plurality of levels of a plurality of pathway perturbations to said patient;- b) determining a plurality of cellular constituent responses in said patient to obtain perturbation profiles;
- b) applying a plurality of levels of said drug to said patient;
- c) determining a plurality of cellular constituent responses in said patient to obtain a 30 drug response profile;
- d) decomposing said drug response profile to pathway responses using said plurality of perturbation profiles to obtain a drug activity on its target pathway and at least one off-target pathway; and

c) determining an optimal dose, wherein said optimal dose has a relatively high activity on said target pathway and relatively low activity on said off-target pathway relative to other doses.

5 60. The method of claim 59 wherein said cellular constituents are transcripts of genes.

61. The method of claim 59 wherein said cellular constituents are proteins.

62. The method of claim 59 wherein said plurality of levels of said drug and pathway
10 3 perturbations are non-toxic to said patient.

15 63. A computer system comprising a processor, and a memory encoding one or more programs coupled to the processor, wherein the one or more programs cause the processor to perform a method, said method comprising comparing activity of a drug against the drug's target pathway (D_{target}) in a biological sample and activity of said drug against at least one off-target pathway ($D_{off-target}$) in said biological sample.

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